Scientific Research Publishing

World Journal of Neuroscience, 2019, 9, 113-137
http://www.scirp.org/journal/wjns
ISSN Online: 2162-2019
ISSN Print: 2162-2000

A Multicenter, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Long-Acting Injectable Formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) for Cocaine Relapse Prevention

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How to cite this paper: Kadric, S., Mohler, H., Kallioniemi, O. and Altmann, K.H. (2019) A Multicenter, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Long-Acting Injectable Formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) for Cocaine Relapse Prevention. *World Journal of Neuroscience*, **9**, 113-137.
https://doi.org/10.4236/wjns.2019.93008

Received: June 15, 2019
Accepted: July 22, 2019
Published: July 25, 2019

Abstract

Objective: To determine the efficacy and tolerability of a long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) for treatment of cocaine-dependent patients. **Design, Setting, and Participants:** A 12-week, A multicenter, randomized, placebo-controlled trial conducted between June 2009-July 2011, at 17 Hospital-based drug clinics, in the 15 countries. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 cocaine use disorder. Of the 2800 patients who were assessed between March 10, 2009 to August 10, 2010, 2600 (93%) were eligible and willing to take part in the trial and were enrolled: 1300 were randomly assigned to receive injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks and 1300 to receive Placebo injections, given intramuscularly once in 12 weeks. Only 100 of 2800 patients (3.6%) did not meet the inclusion criteria. **Main Outcomes and Measures:** The primary endpoints (protocol) were: Confirmed Cocaine abstinence (percentage *i.e.* the number of patients who achieved complete abstinence during 12 weeks). Confirmed abstinence or "cocaine-free" was defined as a negative urine drug test for cocaines and no self-reported cocaine use. Secondary end points included a number of days in treatment, treatment retention and craving. The study also investigated, on 275 participants, degree and time course of Central Dopamine transporter receptor occupancy following single doses of long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) as well as the plasma concentration of Vanoxerine and 17-hydroxyl Vanoxerine. Safety was assessed by adverse

event reporting. **Results:** Of 2600 participants, mean (SD) age was 28.5 (±5.5) years and 598 (23%) were women. 1300 individuals were randomized to receive injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) and 1300 to receive injections of Placebo. 1417 participants (54.5.0%) completed the trial. **Primary Endpoints: Confirmed Cocaine Abstinence:** Complete abstinence was sustained by 72% (n = 936) of Vanoxerine patients (patients treated with Vanoxerine Consta 394.2 mg, long-acting depot formulations) compared with 37% (n = 481) of patients treated with Placebo, during weeks 5 - 12. The difference was significant as evaluated using a Chi-square test (χ^2 = 672.34, P < 0.0001). **Secondary Endpoint: Craving:** A statistically and clinically significant reduction in cocaine craving was observed with Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placeboby week 4 (P = 0.0048), which persisted every week through 12 (P < 0.0001). Patients given Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) had a 87% decrease in craving from baseline to 12th week. Patients given a Placebo had a 2% increase in craving from baseline to 12th week. **Secondary Endpoint: Treatment Retention:** Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) helped significantly more patients complete 12 weeks treatment (n = 936, 72%) compared with Placebo (n = 481, 37%) (χ^2 = 635.53, P < 0.0001). Patients on the long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) had longer treatment retention than patients on Placebo. **Concentrations of Vanoxerine and 17-Hydroxyl Vanoxerinein Plasma:** Analyses were made of 275 study samples. There was no statistically significant difference for plasma Vanoxerine concentrations between days 2 and 84 (p = 0.416). The plasma concentration of Vanoxerine were 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively. Plasma levels of Vanoxerine remained above 70 ng/ml for approximately 12 weeks after administration of Vanoxerine, long-acting depot formulations (Vanoxerine Consta 394.2 mg). **PET Assessments:** Very high central dopamine transporter receptor occupancy by Vanoxerine was detected 1 day after treatments, at which time point the occupancy was 100.0% after Vanoxerine injection (Vanoxerine Consta 394.2 mg). At days 7, 28, 56 and 84 post-Vanoxerine Consta 394.2 mg administration, occupancies were 95% to 79%. Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) led to very high occupancy of Central Dopamine transporter receptors in all brain areas examined; nucleus accumbens, caudate nucleus and putamen. Depending on the brain area Central Dopamine transporter receptor occupancy varied between 95.0% and 79% at days 7, 28, 56 and 84 after dosing. High Vanoxerine occupancy (77%) persisted at 12 weeks after the dosings. **Adverse Reactions:** Adverse events were similar in cocaine-dependent patients treated with the long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) vs. patients treated with Placebo. **Conclusions and Relevance:** Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) were more effective than Placebo injection in maintaining short-term abstinence from cocaine and should be

considered as a treatment option for cocaine-dependent individuals.

Keywords

Vanoxerine Consta, Long-Acting Depot Formulations of Vanoxerine, Cocaine Dependence, Long-Term Delivery, PLGA Polymers

1. Introduction

Cocaine dependence is a significant public health problem that is characterized by recidivism and associated with serious medical, psychiatric, social, and economic consequences [1]. This highly-addictive drug initially produces euphoria. Often, users become psychotic, violent, and suicidally depressed [2]. Safe and effective means of counteracting drug abuse are needed. Although proven pharmacotherapies are available for alcohol and heroin dependence none exist for cocaine dependence despite two decades of clinical trials primarily involving antidepressants, anticonvulsants, and dopaminergic medications [3] [4] [5].

Although many compounds have been evaluated for the treatment of cocaine dependence, none has been approved for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence [6]. Current strategies to treat cocaine dependence include: 1) blocking its effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying conditions (or consequences of use) that may predispose targeted subpopulations toward dependence. An effective pharmacotherapy has long been sought to improve treatment outcomes, particularly since this disorder has a significant neurobiological basis. The mesolimbic dopamine is a crucial neurochemical mediator of rewarding behaviors, e.g., eating and sex [7]. *In vivo* microdialysis studies have demonstrated that the level of extracellular dopamine increases in the nucleus accumbens by people engaged in rewarding behavior, such as or cocaine self-administration. It is believed that the ability of a drug to elevate the level of mesolimbic extracellular dopamine is critical to its abuse and those drugs that inhibit dopamine reuptake, thereby resulting in addictive and euphorogenic effects, are classified as "type 1 blockers" [8]. Increased use of cocaine in the 1980s resulted in a parallel increase in cocaine use by cocaine-dependent and methadone-maintained patients. The increase in the use of cocaine has been further compounded by the link between intravenous drug abuse and the spread of HIV. Consequently, public awareness of drug abuse has increased, leading to drug abuse treatment becoming a national priority in many countries. Accordingly, there is a constant and ever growing need for pharmacotherapies, which enable the treatment of larger numbers of drug abusers than would otherwise be possible with nonpharmacological treatment modalities and which can be coupled with more traditional treatment approaches, such as counseling and rehabilitation [9]. One pharmacotherapeutic approach is to develop a competitive

cocaine antagonist, *i.e.*, a drug that will bind to the dopamine transporter but will not inhibit dopamine reuptake [10]. Such a cocaine antagonist would be expected to block cocaine from increasing the level of extracellular dopamine. However, a patient could overcome the inhibitory effect of a competitive cocaine antagonist by self-administering more cocaine. Another pharmacotherapeutic approach is to develop a noncompetitive cocaine antagonist. The noncompetitive cocaine antagonist would be one that binds to the dopamine transporter with high affinity and dissociates slowly. The noncompetitive cocaine antagonist would then provide a sustained increase in the level of extracellular dopamine, thereby providing the drug abuser with some relief from cocaine-craving due to dopamine deficiency yet inhibiting cocaine from further elevating the level of extracellular dopamine and increasing the probability of increased toxic side effects [11]. One such noncompetitive cocaine antagonist is the compound 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine, otherwise known as Vanoxerine. Vanoxerine is a selective inhibitor of dopamine reuptake and is about 700-fold more potent than cocaine in inhibiting dopamine reuptake in vitro. Unlike cocaine, however, vanoxerine-inhibited dopamine reuptake does not result in addictive and euphorogenic effects and, thus, vanoxerine is considered to be a "type-II blocker". In addition, although cocaine and vanoxerine produce equivalent motor-stimulating effects, vanoxerine must occupy the dopamine transporter to a greater extent than cocaine in order to produce equivalent behavioral effects. Similarly, although cocaine and vanoxerine cause dose-related elevations in extracellular dopamine when given alone, cocaine causes a rapid and short-lived increase in dopamine, whereas vanoxerine causes a low and sustained elevation of dopamine [12].

Currently, there are no available drugs that will effectively block the acute effects of cocaine. We have shown that (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine, known as Vanoxerine, acts as a cocaine antagonist. The study shown here provides a means to block the acute effects of cocaine [13]. By decreasing or limiting the "high" effect of dosing with euphoria-producing drugs, the method of treatment can counteract cocaine intoxication and prevent relapse into drug use during and after treatment. It has been demonstrated that l-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine dihydrochloride (Vanoxerine) act as a cocaine antagonists [14]. Vanoxerine has been used as dopamine agonists for the treatment of Parkinsonism, acromegaly, hyperprolactinemia and diseases arising from a hypofunction of the dopaminergic system [15]. However, the method of the study using Vanoxerine and analogs thereof as cocaine antagonists had not been known previously. Methods are disclosed for treating cocaine addiction, acute effects of cocaine, and cocaine craving. The methods of treatment can counteract cocaine intoxication and prevent relapse into drug use during and after treatment. Safe and effective means of counteracting drug abuse are needed. The studies disclosed herein provides a means for blocking the acute effects of such drugs [16]. By decreasing or limiting the "high" effect

of dosing with euphoria producing drugs, the method of treatment can counteract cocaine intoxication and prevent relapse into drug use during and after treatment. Although drug treatments for cocaine craving are available, there are currently no drugs available which will effectively block the acute effects of cocaine. The drug, Vanoxerine Consta®, presented in this study acts as a cocaine antagonist. We believe that the ability of Vanoxerine Consta® to bind tightly to, and dissociate slowly from, the dopamine reuptake complex, is the underlying mechanism responsible for its cocaine antagonist activity. It has been demonstrated that Vanoxerine Consta® act as a cocaine antagonist for extended intervals, ranging from a few weeks to 3 months [17]. The present study provides sustained-release derivatives of hydroxylated analogs of substituted 1-[2-[bis(aryl)methoxy]ethyl]-piperazines known as Vanoxerine, pharmaceutical compositions comprising the same, and a method of using such sustained-release derivatives to bind the dopamine transporter to achieve a desired effect, such as antagonism of dopamine reuptake inhibitors, such as cocaine, or dopamine releasers or norepinephrine and/or serotonin reuptake inhibitors, such as methamphetamine [18]. Since it is believed that the inhibition of DA reuptake is thought to be the major neurochemical mechanism responsible for the addictive properties of cocaine, PCP, amphetamine and methamphetamine, these agents also interact with the reuptake carriers for serotonin and norepinephrine. The treatment of these addictions is also within the scope of our research wherein treatment effects the DA reuptake complex since these drugs also bind tightly (reversibly or irreversibly) to the serotonin or norepinephrine reuptake carriers [19].

Vanoxerine Consta® is supplied as a microsphere formulation of Vanoxerine [20]. The active ingredient in Vanoxerine Consta®—Vanoxerine—is an antagonist of dopamine transporter (DAT1) with Ki value of 16.9nM. Vanoxerine is a potent and selective dopamine reuptake inhibitor (DRI). Vanoxerine binds to the target site on the dopamine transporter (DAT) ~50 times more strongly than cocaine but simultaneously inhibits the release of dopamine [21]. This combined effect only slightly elevates dopamine levels and block the rewarding effects of cocaine. Vanoxerine is one of the most potent inhibitors of dopamine (DA) reuptake, binds persistently to the DA transporter, resulting in a modest increase in the extracellular levels of DA (ECDA) in the caudate nucleus, as well as an attenuation of the ability of cocaine to elevate ECDA levels [22]. Vanoxerine blocker' the acute effects of cocaine, and the effect occurs immediately after drug administration. Vanoxerine is chemically designated 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine [23].

Long-Acting Injection Vanoxerine Consta® is a combination of extended-release microspheres Vanoxerine for injection. Vanoxerine is micro-encapsulated in 7011 - 18,819 polylactide-co-glycolide (PLG). Over the years, several polymers have been evaluated for the development of controlled release injectable formulations [24]. Of these polymers, one class of polymers has achieved significant commercial success in the pharmaceutical market. The polylactide (PLA) and polylactide-co-glycolide

(PLGA) class of polymers are biodegradable, biocompatible, and nontoxic and have a long history of use [25]. *In vivo*, they are hydrolyzed into metabolic products that are easily eliminated from the body. Initially approved for surgical use in humans they have since been used to formulate a wide range of therapeutic agents. PLGA polymers are well suited for controlled delivery of drugs via the parenteral route as they exhibit good mechanical properties and demonstrate predictable degradation kinetics. Notably, polymeric microspheres prepared using PLGA have been successful in ensuring the sustained release of therapeutic agents for various drugs [26]. Several examples in the literature discuss their effectiveness in providing targeted drug levels *in vivo*, for long periods of time. For this reason, they are popular as delivery vehicles for drugs where the sustained release is desired for extended intervals, ranging from a few weeks to 12 months [27]. The success of PLGA polymers as delivery systems is due to the fact that polymer properties are well understood and can be customized to afford sustained drug release. For instance, selection of copolymers of various lactide: glycolide with variable molecular weights is an effective way to control polymer degradation rate and drug release. By changing the composition of lactide or glycolide in the copolymer, a wide range of degradation rates can be obtained. An increase in the more hydrophobic lactide moiety ensures a slower degradation rate of the PLGA polymer leading to the extended duration of drug release [28]. Similarly, utilization of a higher molecular weight copolymer increases degradation times leading to prolonged drug release. Additional properties that can be varied include polymer crystallinity and glass transition temperature. These physical and chemical properties have been well studied and characterized leading to predictable degradation kinetics of the PLGA polymer, *in vitro* and/or *in vivo* [29]. Upon *in vivo* administration of a PLGA based injectable depot, water interacts with the polymer and hydrolysis of the ester bonds commences. As the polymer degrades, its hydrophobicity decreases and the number of hydrophilic hydroxyl and carboxylic acid end groups in the matrix increases. An accumulation of hydrophilic acidic end groups has a two-fold effect: 1) it increases the amount of water incursion into the polymer and 2) initiates autocatalysis of the polymer matrix. Therefore, polymer degradation and, consequently, drug release from PLGA is a very complex and dynamic process. The study presented a report of the results of a 3-month double-blind phase in terms of the effectiveness and safety of Vanoxerine Consta® for the treatment of cocaine dependence.

The results showed efficacy through an adequate and well-controlled study conducted at several locations in Austria, Bulgaria, Canada, Czech Republic, Germany, Portugal, Romania, Russian Federation, Republic of Angola, Republic of Korea, Republic of Serbia, Spain, Ukraine, UK and United States, with supportive evidence from their clinical pharmacology program.

During treatment with Vanoxerine Consta, cocaine desire is reduced, abstinence is supported, and relapses and cocaine consumption decreased. Also, supportive pharmacological studies have demonstrated the blocking of cocaine

effect over 84 days. The depot formulation of Vanoxerine used in the current study provided a safe, effective and long-lasting antagonism of the effects of cocaine.

The data obtained in this study confirm that a persistent Central Dopamine transporter receptor blockade can be induced by a Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) over 84 days.

Pharmacokinetic: Concentrations of Vanoxerine and 17-Hydroxyl Vanoxerinein Plasma

Analyses were made of 275 study sample. The plasma concentration of Vanoxerine was 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80 and 84 after the doses. Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis. 84 days after the administration of Vanoxerine, the plasma concentration of Vanoxerine was at the lower limit of quantification. The maximum plasma concentration of the drug (Cmax) was 12 h after dosing Vanoxerine Consta 394.2 mg. There was no statistically significant difference between plasma concentrations of Vanoxerine and Central Dopamine transporter receptor occupancy by Vanoxerine between days 1 and 84 (medium limit of quantification).

The depot formulation of Vanoxerine used in the current study provided a safe, effective and long-lasting antagonism of the effects of cocaines.

2. Methods

This randomized clinical trial received 2600 patients in a clinical setting for treatment with long-acting injection of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks compared to Placebo injection given intramuscularly once in 12 weeks. The inclusion was discontinued on August 10, 2010, and the last patient monitoring was carried out on July 23, 2011. The study was approved by the State Committee for Medical and Health Ethics, State Medicines Agency and research ethics committees in the participating countries and hospitals. The monitoring study was conducted by publicly funded supervisory authorities in accordance with good clinical practice standards. The participants gave a written informed consent.

2.1. Participants and Setting

Patients were recruited from March 10, 2009 to August 10, 2010 by research staff from 17 hospital clinics and detoxification units in 15 countries. Eligible participants were cocaine-dependent (according to DSM-IV criteria) men or women aged 22 to 34 years. Exclusion criteria were dependence on other drugs or alcohol or serious somatic or psychiatric illness that was considered a contraindication or required therapy that would interfere with participation in the research (Table 1).

Women in reproductive age could not be pregnant or breast-feeding and

Table 1. Criteria.

Ages Eligible for Study	18 Years to 45 Years (Adult, Older Adult)
Sexes Eligible for Study	All
Accepts Healthy Volunteers	No
Inclusion Criteria	Exclusion Criteria
Written, informed consent	Current or history of a major psychiatric illness, other than drug dependence or disorders secondary to drug abuse
18 years of age or older	Meets DSM-IV criteria for dependence on any drugs other than cocaine,
Meets DSM-IV criteria for current cocaine dependence	Physiologically dependent on alcohol and requires medical detoxification
Currently seeking treatment for cocaine dependence	Use of prescription drugs within 14 days prior to study entry
Currently Not uses cocaine, as determined by a self-report and a negative urine test for cocaine, within 30 days prior to study entry	Use of non-prescription drugs within 7 days prior to study entry
Good general health	If female used an oral contraceptive, Depo-Provera, Norplant, or intrauterine progesterone contraceptive system, within 30 days prior to study entry
Normal electrocardiogram	Pregnant or breastfeeding
Noncustodial, stable residence and phone, plus 1 contact with verifiable address and phone	History of liver disease and evidence of hepatic failure
Significant other (eg, spouse, relative) willing to supervise compliance with the study visit schedule and procedures	Current elevated aspartate aminotransferase or alanine aminotransferase levels
Completing or recently completed up to 30 days of inpatient treatment for cocaine detoxification for at least 7 days	Participated in any other clinical investigation within 4 weeks prior to study entry
Able to provide written informed consent	History of any illness or behavior that, in the opinion of the investigator, might interfere with the study
Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study	Family history of early significant cardiovascular disease
	Clinically significant medical condition or observed abnormalities (eg: physical exam, electrocardiogram (ECG), lab and/or urinalysis findings)
	Current major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the ability to complete the study
	Known intolerance and/or hypersensitivity to vanoxerine or polylactide-co-glycolide (PLG)

agreed to use effective birth control. Participants were screened for psychiatric disorders and examined for severe somatic illness. Routine blood tests (complete blood cell counts, electrolytes, and levels of ALT/AST) and urinalysis were completed as part of usual treatment before study enrollment. Assessments added for the study included a detailed history of drug use and psychiatric interview to confirm current cocaine dependence; urine testing for cocanie and alcohol breath test; Addiction Severity Index; pregnancy test; monthly measurements of ALT and AST levels while receiving medication; cocaine craving (visual analog scale); Global Assessment of Functioning; Brief Psychiatric Rating Scale; and visual inspection of the site 5 to 7 days after implantation (Table 2). Urine drug testing was performed at biweekly counseling sessions.

Table 2. Lifetime and baseline clinical characteristics of participants randomized into treatment groups.

	long-acting Vanoxerine (Vanoxerine Consta 394.2 mg) (n = 1300)	Placebo (n = 1300)
Age in years	28.5 (±5.5)	27.2 (±4.6)
Men	858 (66%)	897 (69%)
Female	442 (34%)	403 (28%)
Marital status	No. (%)	No. (%)
Never married	403 (31%)	429 (33%)
Married/de facto	650 (50%)	715 (55%)
Divorced/separated	247 (19%)	156 (12%)
Race	No. (%)	No. (%)
White	943(72.5%)	1021 (78.5%)
Asian	26 (2%)	26 (2%)
Black	234(18%)	234 (18%)
Others	97 (7.4%)	19 (1.5%)
Employment status	No. (%)	No. (%)
Student	182 (14%)	247 (19%)
Employed (full/part time)	689 (53%)	650 (50%)
Unemployed/pension	429 (33%)	403 (31%)
Duration of cocaine dependence in years	6.1 (±3.5)	6.0 (±3.5)
Distribution of Duration of cocaine Dependence	No. (%)	No. (%)
<1 year	130 (10%)	143 (11%)
1 - 3 years	286 (22%)	299 (23%)
3 - 5 years	715 (55%)	676 (52%)
>5 years	169 (13%)	182 (14%)
Cocaine craving scale	20 (±2)	20 (±2)
Hepatitis C positive	169 (13%)	195 (15%)

Eligible participants were referred to the detoxification unit after examination and inclusion. The study took place at the hospital facility, and all participants were discharged from the detoxification unit and are in the process of hospital treatment. Ethnicity is defined by the participants.

2.2. Procedure and Outcomes

After detoxification, participants were randomly assigned (1:1) to commence either administration of injections of Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) given intramuscularly once in 12 weeks or administration of injections of Placebo given intramuscularly once in 12 weeks. Allocation to treatment group was computerized using a permuted block algorithm provided by the state monitoring authority and not stratified for site or sex. Following induction into either medication regimen, participants were asked to attend standard drug counseling, but no behavioral interventions could

be initiated. At baseline (inclusion) and every 4 weeks thereafter, patients underwent a structured interview using the European version of the Addiction Severity Index covering drug use, physical and mental health, work, education, and criminal activity.

Primary outcome variables Confirmed Cocaine abstinence (percentage *i.e.* the number of patients who achieved complete abstinence during week 12) or "cocaine-free" was defined as a negative urine drug test for cocaines and no self-reported cocaine use. The twice a week UDTs were analyzed using specific chromatographic methods and calculated as the number of cocaine-negative urine drug screens divided by the total number of attended tests (group proportion) in accordance with recently revised Cochrane guidelines. Missing UDTs were considered as testing positive for cocaines in all participants. Secondary outcome variables were comparison of retention in the study, number of days in treatment, the degree of cocaine craving (Minnesota Cocaine Craving Scale (MCCS): Composed of five items which correspond to intensity, frequency, duration of craving, changes in relation to previous week and craving response to medication), and mental health (Hopkins Symptom Checklist-25 of anxiety and depression, 25 - 100, with 25 indicating very low; 100, very high). Retention in treatment was defined as the number of days until dropout from study medication and by the number of patients completing the study at week 12. Participants who completed this randomized clinical trial were invited to continue or cross over to either treatment for up to 48 weeks. These data will be described in a subsequent publication.

2.3. Pharmacokinetic Studies: The Plasma Concentration of Vanoxerine and Plasma Concentrations of Vanoxerine-3-O-Glucuronide

Analyses were made of 275 study sample. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80 and 84 after the doses.

2.4. Pharmacokinetic Studies Protocol

Blood samples were collected through an indwelling plastic cannula, inserted into a superficial upper arm vein, into tubes containing anticoagulant Li-heparin. They were drawn at given time points, centrifuged, and plasma was separated within 1 h of sampling. The plasma specimens were frozen at −20˚C or colder until analyzed. Vanoxerine and 17-hydroxyl Vanoxerine were extracted from plasma with ethyl acetate. The organic layer was transferred to clean tubes and evaporated to dryness. The residue was reconstituted in the mobile phase and aliquots were injected into a high-pressure liquid chromatography-mass spectrometry system. Two analyses were made of each study sample: determination of intact Vanoxerine and Vanoxerine-3-O-glucuronide, and determination of total concentration of the analytes. A set of plasma standards containing 40 - 120 ng/ml of Vanoxerine and 17-hydroxyl Vanoxerine in drug-free plasma was used to construct a calibration curve for each batch of plasma samples. Four quality control

samples containing 40, 60, 80, and 120 ng/ml of Vanoxerine and 17-hydroxyl Vanoxerine were analyzed in duplicate in each batch of study samples. The inter-batch precision (CV%) for Vanoxerine was from 4.3% to 7.3% and for 17-hydroxyl Vanoxerine from 4.3% to 10.8%. Total concentration was analyzed with calibration range from 25 to 150 ng/ml. Two spiked and two pooled control samples were analyzed in duplicate in each sample batch. The spiked control samples (40 and 120 ng/ml) were made by spiking drug-free plasma with Vanoxerine and 17-hydroxyl Vanoxerine solutions to contain known concentrations of the analytes. The pooled controls were made by pooling plasma of previously analyzed study samples. Concentrations of Vanoxerine in plasma pools were 71 and 94 ng/ml and concentrations of 17-hydroxyl Vanoxerine 10.5 and 13.2 ng/ml, respectively. The spiked plasma controls indicated the stability of intact analytes under analytical conditions. The inter-batch precision (CV%) was from 2.8% to 6.8% for Vanoxerine and from 4.2% to 6.6% for Vanoxerine-3-O-glucuronide. Pharmacokinetic variables of Vanoxerine and 17-hydroxyl Vanoxerine were determined from the concentration-time data by the PCNONLIN software using noncompartmental methods. Peak concentration (Cmax), taken as the maximum observed concentration in plasma, and time to peak concentration (Tmax) were observed. After injection of Vanoxerine Consta 394.2 mg, area under the plasma concentration-time curve from time zero to infinity (AUC) was calculated by the trapezoidal rule to the last observed concentration with extrapolation to infinity by dividing the last observed concentration by the elimination rate constant. The effect of minor deviations from the planned blood sampling times in the pharmacokinetic analysis was cancelled out by using actual sampling times in calculations.

2.5. PET Studies

275 subjects participated in PET studies, and they were scanned before Vanoxerine Consta 394.2 mg administration in order to obtain quantitative baseline data of Central Dopamine transporter receptor distribution. Thereafter, the subjects were assigned for PET imaging at 24 h and day 12, 36, 60, or 84 after single Vanoxerine administration. 275 lead ECG was obtained at screening, and before and at 3 h after Vanoxerine administration on the first dose day and the last treatment day. Safety and tolerability monitoring were performed throughout the study.

2.6. PET Studies Protocol

Dopamine transporter receptor occupancies were measured at day 2, 12, 36, 60, or 84 after single Vanoxerine administration (by using a carbon-11-labeled imaging agent (Altropane) and positron emission tomography). A highly sensitive method has been developed to measure drug occupancy of the dopamine transporter in the brain by using a carbon-11-labeled radioligand (Altropane) to label the dopamine transporter and positron emission tomography (PET) for detection. Because the time course of decay of the carbon-11 isotope permits repeated imaging, this method allows examination of the kinetics of CNS dopamine

transporter receptor occupancy in the living human brain. Subjects underwent PET imaging before and at day 2, 12, 36, 60, or 84 after single Vanoxerine Consta administration. Subjects underwent a total of five PET imaging sessions on five different days. On day 1, baseline scanning (one scan) was completed. Images were acquired by using an HR+ PET camera. The primary imaging parameters of the HR+ camera are the in-plane and axial resolution of 4.5 mm full width at half maximum and 63 contiguous slices of 2.5-mm separation. Images were acquired in three-dimensional mode and reconstructed by using an iterative algorithm to an in-plane resolution of 4.5 mm full width at half maximum. Photon attenuation measurements were made with rotating pin sources containing germanium-68. For each scan, approximately 5 mCi of carbon-11-labeled radioligand was injected intravenously over 30 seconds, and serial PET images were acquired. Dynamic image collection started at the same time as the infusion, and images were acquired in 15-second frames for the first 2 minutes, in 1-minute frames for the next 4 minutes, and in 2-minute frames for the last 54 minutes, for a total of 39 frames over 60 minutes. On the other days of scanning the radioligand injection and imaging procedures were repeated. All projection data were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. Regions of interest represent nucleus accumbens, caudate nucleus and putamen. This procedure was repeated for all slices in which the structures were visualized at full intensity (away from edge slices. The binding potential values (BP, or Bmax/Kd) for the carbon11-labeled radioligand were calculated by using a kinetic model that compared data from the striatum and cerebellum. In the regional analysis, integrated images of each of the dynamic PET scans were realigned, and the obtained mean PET image was coregistered with the MRI for each subject. All realignment and coregistration procedures were performed using Statistical Parametric Mapping software version 99 (SPM99). The regions of interest (ROIs) were manually drawn in the nucleus accumbens, caudate nucleus, and putamen of the coregistered MRIs using the Imadeus software (Imadeus Academic 1.10 (Forima Inc.)) for the calculation of regional time-tissue radioactivity concentration curves. The simplified reference tissue model shown to be insensitive to changes in blood flow was applied in the derivation of Central Dopamine transporter receptor binding potential (BP; denotes k3/k4 in this study) values from the regional time-radioactivity concentration curves. The cerebellum was used as the reference region. The reduction in the amount of Central Dopamine transporter receptors available for carbon-11-labeled imaging agent (Altropane) binding after Vanoxerine Consta 394.2 mg administration was calculated as the decrease in the BP of carbon-11-labeled imaging agent (Altropane) upon Vanoxerine treatment (BPVanoxerine) in comparison with pre-drug baseline level (BPBaseline) according to Equation 1. To visualize the distribution of BP values and Central Dopamine transporter receptor occupancy by Vanoxerine, a voxel-based image analysis of the data was performed. Parametric images for the whole brain were calculated

using the Matlab 6.5 and Receptor Parametric Mapping software, based on the simplified reference tissue model. Realignment and spatial normalization of BP images were made using the SPM99 to enable the presentation of the results in the common stereotactic space.

2.7. Statistical Analysis

The target sample size was based on the width of the 95% CI for the hazard ratio (HR) of the difference between treatments (Vanoxerine *vs* Placebo), projecting relapse-free survival of about 50% for each medication after induction. On the basis of simulation results, the 95% CI width for HR decreases as the sample size increases by 120 per group to 720 per group (from a base of 400 per group) by 31%, 19%, 14%, and 11%, respectively. A preplanned interim analysis increased the overall target sample size from an initial 1000 participants to about 1600 participants to achieve a minimum sample of 950 participants in the late randomisation group. Sample size calculations indicated that 950 participants would yield a similar (only slightly wider) 95% CI to the original sample size target of 1000 participants, and preserved the aim to achieve a precise estimate of the difference in relapses between groups. We analysed endpoints according to the intention-to-treat principle as part of the primary analysis and additionally among a per-protocol population.

The per-protocol population consisted of only those participants who were successfully inducted onto an initial dose of study medication. The primary outcome analysis was the construction of the asymptotic 95% CI for the HR of the difference between the treatment groups among the intention-to-treat population in the time-to-event (relapse) distribution with the earliest relapse day assessed at day 21. We administratively censored participants at week 12. The binary baseline covariate of early versus late randomisation was examined for an interaction with treatment; this covariate was not significant ($p > 0.10$), and thus dropped from the final model. Unadjusted Kaplan-Meier survival curves and the extended Cox model HRs compared relapse by group. We examined the proportional hazard assumption via the interaction of treatment and time. Logistic regression yielding odds ratios contrasted induction success and overall 12-week cocaine relapse by group. We used Pearson's χ^2 or Fisher's exact tests, and logistic regression for analyses of dichotomous secondary outcomes. We used Cox models for time-to-event secondary outcomes and Wilcoxon rank-sum tests and mixed effects models for continuous outcomes. We considered missing urine samples to be cocaine positive and contributed to the definition of a relapse event. Thus, treatment dropouts (who stopped contributing data) were scored as having relapsed, an assumption which is likely in this population. Adverse events were compared using Fisher exact test. Retention in treatment was assessed by a log rank test. The results at $P < 0.05$ were considered significant in all superiority analyses. The noninferiority analyses were assessed by 1-sided test at the same significance level. Statistical analyses were conducted by a study-independent statistician blinded to the names of the study medications. The analyses were

performed in SPSS, version 24 (SPSS Corp) and SAS, version 9.4 (SAS Institute).

Pharmacokinetic parameters ($AUC_{T,\infty}$, C_{max}) were analyzed using repeated measures analysis of variance. Natural logarithm transformation was used for these variables in order to achieve normality, if needed. No additional covariates were used in the statistical model. Time to peak concentration (t_{max}) of each period was analyzed using a Wilcoxon signed-ranks test. Terminal half-life ($t_{1/2}$) was analyzed using repeated measures analysis of variance or Wilcoxon signed-ranks test, depending on the distribution. The limit of statistical significance for all analyses was set at $p < 0.05$, and 90% confidence intervals for the ratios of geometric means (Vanoxerine Consta 394.2 mg/Placebo, Placebo380 mg) were calculated. Occupancy and safety variables were analyzed by descriptive statistics. Statistical analyses were performed with the SAS for Windows version 9.4 (SAS Institute).

3. Results

3.1. Patient Characteristics

Men and women displayed similar age distributions, 28.5 (±5.5 and 27.2 (±4.6) years, respectively), years of heavy cocaine use (mean, 3.5 (±2.5) and 2.0 (±0.9) respectively and other social characteristics. 75% (±3) of the participants were white. 14% (±1) participants tested seropositive for hepatitis C (**Table 1**, **Table 2**).

3.2. Retention in Treatment

Among the 2800 participants assessed for eligibility, 2600 were included in the study and 1300 were randomized to treatment with Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) (n = 1300, 50%) or Placebo (n = 1300, 50%) (**Figure 1**).

Reasons for exclusion of 200 individuals were not meeting inclusion criteria (100 [50%]), failed detoxification (70 [35%]) and other reasons (30 [15%]). Among the randomized participants, 2600 agreed to commence their medication: 1300 (50%) in the Long-acting intramuscular formulation of Vanoxerine group and 1300 (50%) in the Placebo group. Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) helped significantly more patients complete 12 weeks treatment (n = 936, 72%) compared with Placebo (n = 481, 37%) ($\chi^2 = 635.53$, $P < 0.0001$) (**Figure 2**). Of the Vanoxerine Consta 394.2 mg group that began the study, 72% (936/1300) completed the full 12 weeks of treatment compared to Placebo group where 37% (481/1300) completed the full 12 weeks of treatment. Patients on long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) had longer treatment retention than patients on Placebo (**Figure 3**).

3.3. Primary Endpoints: Confirmed Cocaine Abstinence

Complete abstinence was sustained by 72% (n = 936) of Vanoxerine patients (patients treated with Vanoxerine Consta 394.2 mg, long-acting depot formulations) compared with 37% (n = 481) of patients treated with Placebo, during weeks 5 - 12. The difference was significant as evaluated using a Chi-square test

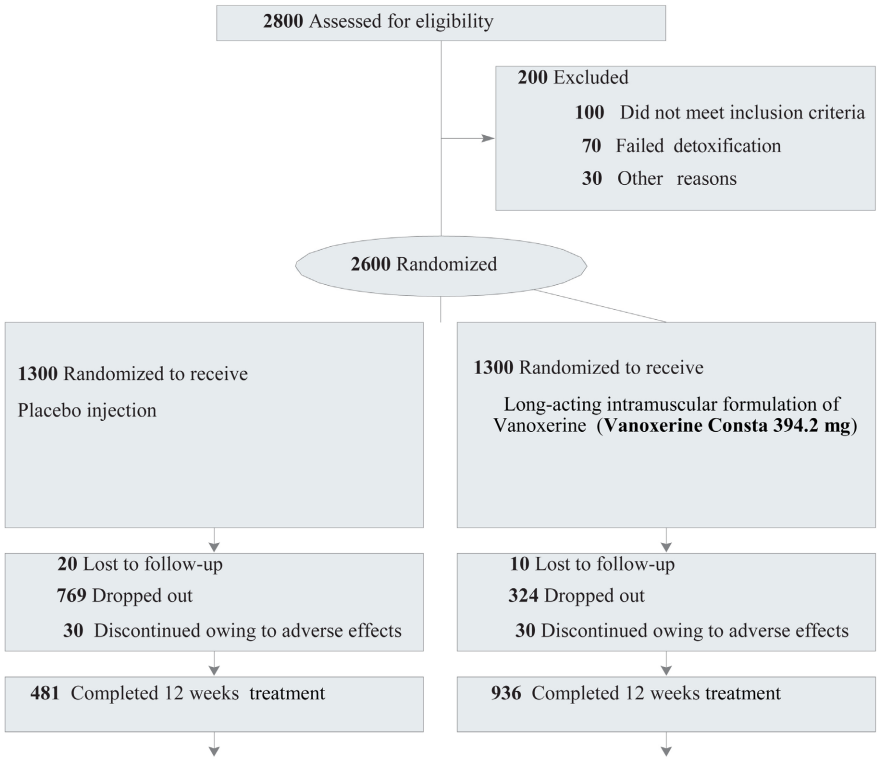

Figure 1. Flowchart for inclusion of participants.

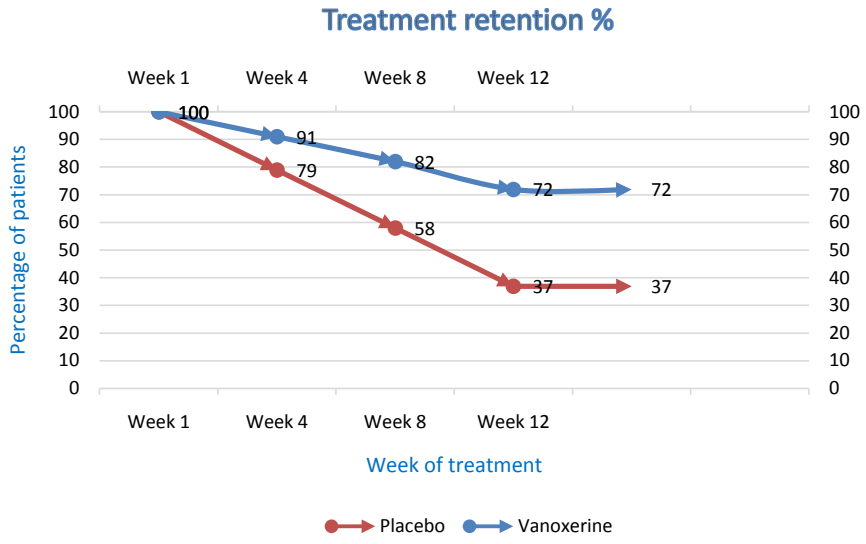

Figure 2. Survival curves for retention in treatment. *percentage of participants through the number of days in the treatment.

(χ^2 = 672.34, P < 0.0001) (**Figure 4**). *(Percentage of cocaine-free patients through weeks 5 - 12). Confirmed abstinence or "cocaine-free" was defined as a negative urine drug test for cocaines and no self-reported cocaine use. Assessing the superiority of Vanoxerine Consta 394.2 mg treatment over the Placebo showed significant differences between the treatment groups in the proportion of negative UDTs (P < 0.0001). Treatment with Placebo was inferior to Vanoxerine

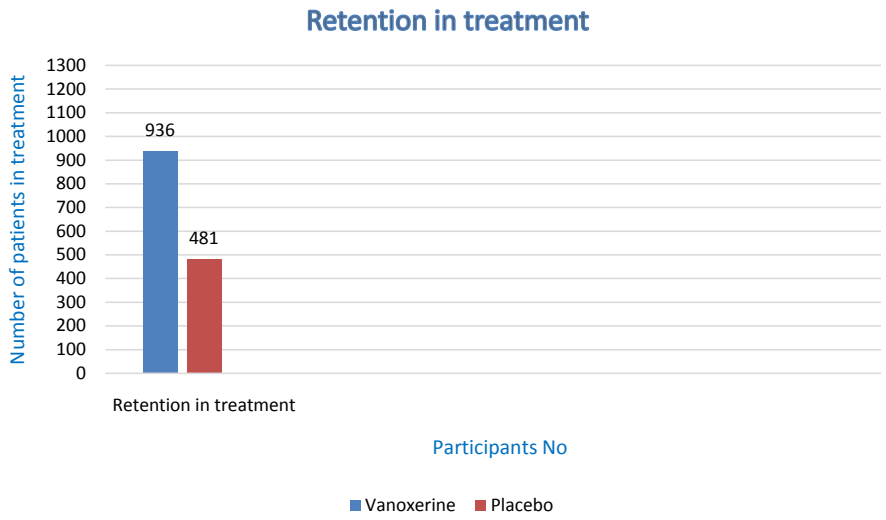

Figure 3. Retention in treatment. *number of participants in the treatment.

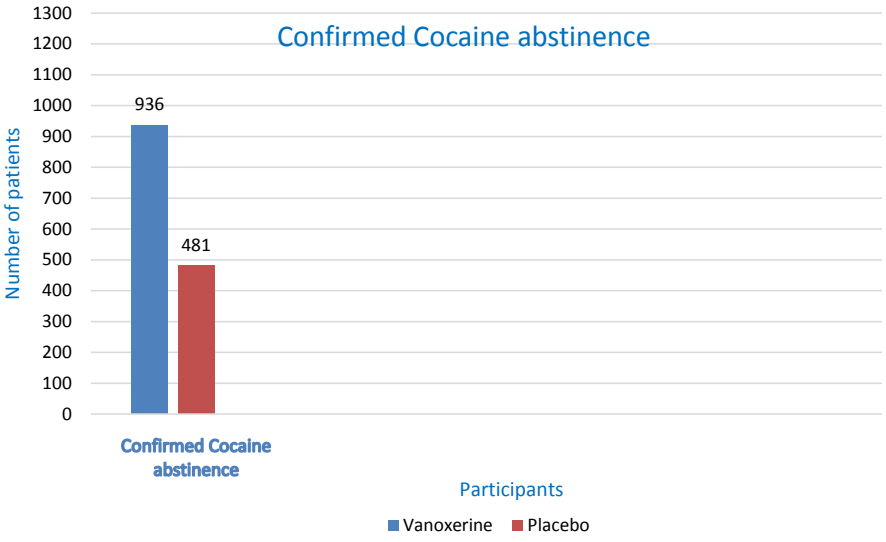

Figure 4. Confirmed Cocaine abstinence.

long-acting depot formulations (Vanoxerine Consta 394.2 mg) regarding the group proportion of the total number of cocaine-negative UDTs.

3.4. Secondary Endpoint: Craving

Craving was reported weekly according to a Minnesota Cocaine Craving Scale (MCCS), composed of five items which correspond to intensity, frequency, duration of craving, changes in relation to previous week and craving response to medication (we used the first three items of the scale (none 0 to 10 maximum visual score analogue scale)).

Reduction in craving intensity was observed in baseline and every week to final evaluation, week 12. A statistically significant finding in this study was a decrease in craving intensity, frequency and duration of craving. A statistically and clinically significant reduction in cocaine craving was observed with Vanoxerine

(Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placebo by week 4 (P = 0.0048), which persisted every week through 12 (P < 0.0001). At all time points, participants receiving long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) reported significantly a decrease in craving intensity, frequency and duration of craving for cocaine than Placebo participants.

Patients given Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) had a 75% decrease in craving intensity, 70% decrease in frequency and 75% in duration from baseline to week 12. Patients given a Placebo injection had a 1% increase in craving from baseline to week 12.

Satisfaction with treatment was significantly higher among Vanoxerine Consta 394.2 mg, long-acting depot formulations) participants and they would also recommend their treatment to others to a higher extent compared with Placebo participants. The main clinical implication of this result is that Vanoxerine Consta seems to reduce craving, which is one of the main factors related to relapses in drug dependence.

3.5. Pharmacokinetic Assessments: Concentrations of Vanoxerine and 17-Hydroxyl Vanoxerine in Plasma

Analyses were made of 275 study sample. Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis, 84 days after the administration long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg). There was no statistically significant difference for plasma Vanoxerine concentrations between days 2 and 84 (p = 0.416). The plasma concentration of Vanoxerine were 70.4 and 94.3 ng/ml and concentrations of 17-hydroxyl Vanoxerine were 10.5 and 13.2 ng/ml, respectively (**Figure 5**). Plasma levels of Vanoxerine remained above 70 ng/ml for approximately 12 weeks after administration long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg).

3.6. PET Assessments

Very high Central Dopamine transporter receptor occupancy by Vanoxerine was

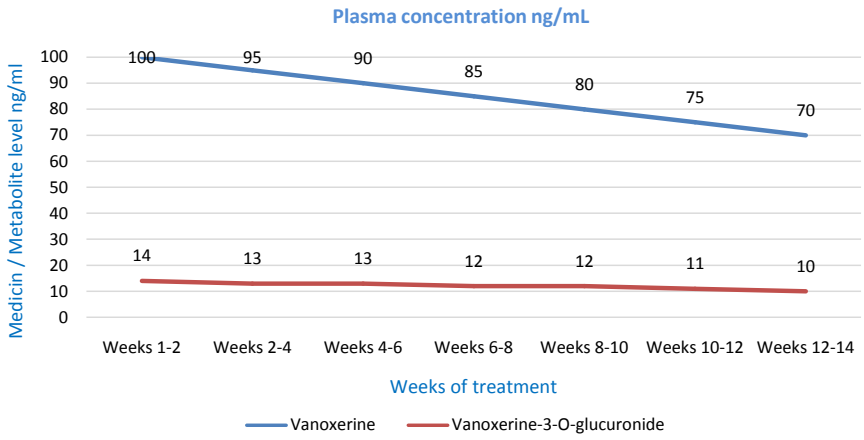

Figure 5. Plasma concentration of Vanoxerine and Vanoxerine-3-O-glucuronide.

detected 1 day after treatments at which time point the occupancy was 100.0% after Vanoxerine injection (Vanoxerine Consta 394.2 mg). At days 7, 28, 56 and 84 post-Vanoxerine Consta 394.2 mg administration, occupancies were 95% to 79%. Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) led to a very high occupancy of Central Dopamine transporter receptors in all brain areas examined; nucleus accumbens, caudate nucleus and putamen. Depending on the brain area Central Dopamine transporter receptor occupancy varied between 95.0% and 79% at days 7, 28, 56 and 84 after dosing. High Vanoxerine occupancy (77%) persisted at 12 weeks after the dosings.

The study investigated, on 275 participants, degree and time course of Central Dopamine transporter receptor occupancy following single 393.1 mg doses of Vanoxerine Consta injection. Very high Central Dopamine transporter receptor occupancy by Vanoxerine was detected 1 day after treatments at which time point the occupancy was 100.0% after Vanoxerine injection (Vanoxerine Consta 394.2 mg). At days 7, 28, 56 and 84 post-Vanoxerine Consta 394.2 mg administration, occupancies were 95% to 79%. Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) led to a very high occupancy of Central Dopamine transporter receptors in all brain areas examined; nucleus accumbens, caudate nucleus and putamen. Depending on the brain area Central Dopamine transporter receptor occupancy varied between 95.0% and 79% at days 7, 28, 56 and 84 after dosing (**Figure 6**). High Vanoxerine occupancy (77%) persisted at 12 weeks after the dosings. The data obtained in this study confirm that a persistent Central Dopamine transporter receptor blockade can be induced by a Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine). High Vanoxerine occupancy (77% - 79%) persisted at 12 weeks after the dosings. The prolonged Central Dopamine transporter receptor occupancy by Vanoxerine indicates slow dissociation of the drug from Central Dopamine transporter receptors.

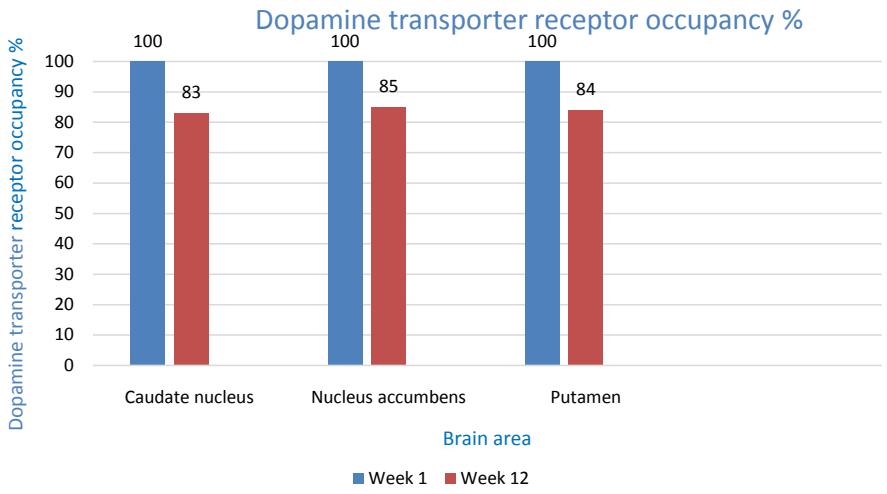

Figure 6. Central Dopamine transporter receptor occupancy.

Vanoxerine Consta 394.2 mg administration resulted in a very high occupancy at Central Dopamine transporter receptors (77% - 100%) and the decline in the occupancy was slower than the decline in the plasma concentration of Vanoxerine or its metabolite.

3.7. Adverse Reactions

Adverse events were similar in cocaine-dependent patients treated with long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) vs. patients treated with Placebo (difference, 0.1 with 95% CI, −0.04 to 0.2; P < 0.001) (Figure 7, Table 3).

Table 3. Adverse events by description.

	long-acting Vanoxerine (Vanoxerine Consta 394.2 mg) (n = 1300)	Placebo (n = 1200)
Alanine aminotransferase increased	2.86 (0.22%)	2.6 (0.2%)
Aspartate aminotransferase increased	2.86 (0.22%)	2.6 (0.2%)
Gamma-glutamyltransferase increased	1.95 (0.15%)	1.95 (0.15%)
Back pain	104 (8%)	91 (7%)
Insomnia	117 (9%)	104 (8%)
Diarrhea	65 (5%)	52 (4%)
Hypertension	52 (4%)	39 (3%)
Injection site pain	104 (8%)	104 (8%)
Dizziness	52 (4%)	39 (3%)
Headache	39 (3%)	26 (2%)
Nervousness	39 (3%)	39 (3%)
Runny nose	39 (3%)	39 (3%)

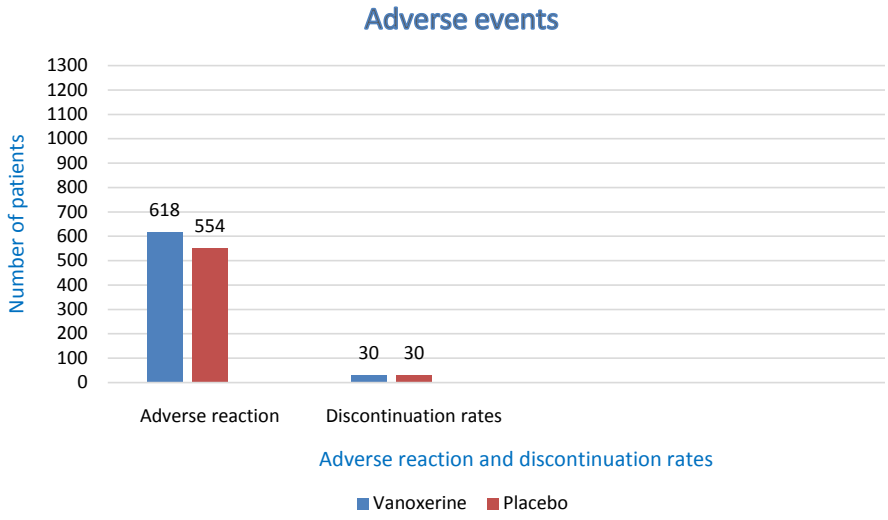

Figure 7. Adverse events.

Discontinuation rates due to adverse events were similar in cocaine-dependent patients treated with Placebo vs. patients treated with Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg (2%). Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was generally well tolerated. It was not associated with increased levels of ALT or AST.

There were no deaths, but 6 (0.4%) Placebo participants and 3 (0.2%) Vanoxerine Consta 394.2 mg participants reported a serious adverse event. All recovered completely and maintained their study medication. Adverse reactions equally occurred in patients with cocaine dependence treated with Placebo and with Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) group.

4. Discussion

To our knowledge, this is the first study comparing the effectiveness of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) with Placebo injections (Placebo 380 mg), the newest treatment for cocaine-dependent patients in many countries. Treatment with long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was more effective than with Placebo in maintaining retention in treatment and craving for cocaines. The main clinical implication of these findings is that long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) seem to be safe and effective than Placebo treatment for maintaining short-term abstinence from cocaine, and other cocaines substances in cocaine-dependent individuals newly detoxified and/or discharged from inpatient treatment. Since we discriminated between cocaine and other illicit cocaines, mainly oral formulations, our data also seem to be clinically relevant for the growing number of individuals who are addicted to prescribed cocaines.

Induction into treatment with long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) required full detoxification to a greater extent than into Placebo treatment. The modern instruction and guidelines for detoxification of cocaine users turned out to be insufficient for study detoxification and frequently produced adverse effects related to withdrawal symptoms on the induction of Vanoxerine Consta 394.2 mg, (long-acting depot formulations of Vanoxerine) and, to some extent Placebo. We, therefore, changed our detoxification strategy during the first year of the study in accordance with the most recent literature at the time of our study which reduced the number of new adverse events related to the induction of treatment. Serious adverse events were equally distributed between the groups and were not directly related to the given treatment, which explains why there were no dropouts among participants reporting a serious adverse event.

Satisfaction with treatment and willingness to recommend their treatment to others were significantly higher among Vanoxerine Consta 394.2 mg, (long-acting depot formulations of Vanoxerine).

A clinically significant reduction in cocaine craving was observed with Vanoxerine (Vanoxerine Consta 394.2 mg, long-acting depot formulations) vs. Placebo. At all time points, participants receiving long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg) reported significantly less cocaine craving and thoughts about cocaine than did Placebo participants.

This finding makes it likely that the majority of participants were mainly motivated to receive the novel long-acting depot injection of Vanoxerine (Vanoxerine Consta 394.2 mg). A treatment with long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) would be very effective in individuals with lower motivation for cocaine abstinence.

There was no reported overdose in the study. This low rate may reflect the high motivation for treatment and good response to regular follow-up by the same study worker in this group of participants. In the present study, several participants used cocaine after receiving the depot injections, but there was no evidence that attempts to override the blockade were successful, and no accidental or intentional cocaine over-doses occurred. It is possible that the gradual dissipation of Vanoxerine from these long-acting injectable formulation (Vanoxerine Consta 394.2 mg) protected these patients from experiencing cocaine overdose.

The results of the study also show the consistency of release of Vanoxerine and on the average level of Vanoxerine between 70.4 and 94.3 ng/mL over the 12, weeks life of the Vanoxerine Consta 394.2 mg. After the administration of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg), mean Vanoxerine plasma levels ranged from 77 and 94 ng/mL. Across the 12-week study, plasma Vanoxerine levels tended to be fairly constant, with perhaps a slight decline during the twelfth week after drug administration. In general, many investigators agree that doses that maintain Vanoxerine plasma levels of approximately 70 ng/mL are sufficient for antagonizing the effects of high doses of cocaine agonists.

Every single dose of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) resulted in very high occupancy at the Central Dopamine transporter receptors (94% to 100%) measured 24 hours post-dose. The high Vanoxerine occupancy (95% to 79%) persisted 10 weeks after single dosing of long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) and the receptor occupancy was still above 77%, 12 weeks after dosing.

Long-acting depot formulations of Vanoxerine (Vanoxerine Consta 394.2 mg) was more effective than Placebo in maintaining short-term abstinence from cocaine and should be considered as a treatment option for cocaine-dependent individuals.

This study demonstrated that a long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) in conjunction with psychosocial treatment significantly reduced cocaine use in a large geographically varied sample of treatment-seeking patients with cocaine dependence. Long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) was well tolerated, few serious

Table 4. Treatment outcomes and complications

Treatment outcomes	long-acting Vanoxerine (Vanoxerine Consta 394.2mg) (n = 1300)	Placebo (n = 1300)	Treatment effect
2800 Assessed for eligibility 2600 Randomized	1300 Randomized to receive Long-acting intramuscular formulation of Vanoxerine (Vanoxerine Consta 394.2 mg)	1300 Randomized to receive Placebo	1417 Completed 12 weeks treatment
Cocaine relapse patients weeks 4 - 12	28% (n = 364)	63% (n = 855)	(P < 0.0001)
Cocaine-free patients weeks 4 - 12	72% (n = 936)	37% (n = 645)	(P < 0.0001)
Retention in treatment	72% (n = 936)	37% (n = 645)	(P < 0.0001)
Adverse reaction and adverse events	47% (n = 618)	42% (n = 554)	(P = 0.04)

adverse events were reported, and there was no evidence of hepatotoxicity. Regarding tissue reactions around the site of injections, the formulation of depot Vanoxerine (Vanoxerine Consta 394.2 mg) used in the present study was well tolerated. In the 20 patients with injection site reactions, the severity was considered to be moderate, and all reactions resolved spontaneously over time.

In summary, the results from this trial, with one of the largest samples ever treated with a medication for cocaine dependence, indicate that long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) is well tolerated and is associated with a significant reduction in cocaine use in the cocaine-dependent population (Table 4). The long-acting formulation has the potential to improve intervention strategies for cocaine dependence by providing a predictable pharmacological foundation for treatment. In addition to their utility for cocaine dependence, long-acting formulations may prove to be an important treatment strategy for a variety of addictive disorders. The present results demonstrate that this long-acting injectable formulation of Vanoxerine (Vanoxerine Consta 394.2 mg) is safe, well tolerated, and effective in retaining patients in treatment. An increase in treatment retention is particularly important because it will allow clinicians sufficient time to engage patients in psychotherapy so that they can learn to make other psychological and social adjustments that support life without cocaines.

Declaration of Interests

All authors report grant or contract funding from the Aurum Charitable Trust. The main staff (doctors, nurses, laboratory assistants), participants in research, as well as their assistants, received other research support from the National Institute for Drug Abuse of their country for this study. Hanns Mohler received other research support from Aurum Pharmaceuticals, and consulting fees from Aurum Pharmaceuticals. All authors declare no competing interests.

This study was sponsored by the Aurum Charitable Trust. We thank all the site research teams, clinical staff, and the most importantly the study participants for their effort and time. This research was supported by grants from the National Institute for Drug Abuse of 15 countries:

Austria, Bulgaria, Canada, Czech Republic, Germany, Portugal, Romania, Russian Federation, Republic of Angola, Republic of Korea, Republic of Serbia, Ukraine, UK and United States, we thank all for understanding and support.

Role of the Funder/Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication; however, Aurum Pharmaceuticals was allowed to comment on the manuscript before submission for publication.

Vanoxerine Consta 394.2 mg injection (long-acting intramuscular formulation of Vanoxerine) was donated free of charge by Aurum Pharmaceuticals.

The trial was conducted in hospital units at:

Klinik Parachute Vienna, Austria, Ayurva drug and alcohol addiction treatment clinic, Bulgaria, Orchard Recovery Center addiction treatment clinic, Canada, Clinical department of the Centre for Addictology, Czech Republic, Betty Ford Klinik GmbH, Germany, Dianova Portugal International Addiction Treatment Centre, Portugal, Clinica ALIAT, Addiction Treatment Center, Romania, Drug Addiction Treatment Center (Narcology), Russian Federation, Specialized treatment services for drug and alcohol addiction, Republic of Angola, Boramae Medical Center, Republic of Korea, Special Hospital for Alcohol and Drug Dependence, Republic of Serbia, The Narconon Center, Ukraine, Priory Addiction Treatment Centers, United Kingdom, Priory Clinic Canterbury, Priory Hospital North London, Drug and alcohol addiction treatment center Betty Ford, United States, Mayo Clinic drug and alcohol addiction, United States.

We thank all study site personnel for their efforts, as well as all participating patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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